REMARKS

Reconsideration of this Application is respectfully requested.

Upon entry of the foregoing amendment, claims 1-3 and 8-19 are pending in the application. These changes are believed to introduce no new matter, and their entry is respectfully requested.

In the Office Action of November 23, 2001, the Examiner set forth a number of grounds for rejection. These grounds are addressed individually and in detail below.

Rejections Under 35 U.S.C. § 101 and 35 U.S.C § 112, Second Paragraph

Claims 4-7 stand rejected under 35 U.S.C. § 101 and 35 U.S.C. § 112, second paragraph, because the claimed recitation of a use, without setting forth any steps involved in the process.

moot

In response, Applicants have canceled claims 4-7 and added claims 8-19. The grounds for this rejection have been obviated and thus, withdrawal of the 35 U.S.C. § 101 and 35 U.S.C. §112, second paragraph, rejections is respectfully requested.

Rejection Under 35 U.S.C. § 102

Claims 1-3 stand rejected under 35 U.S.C. § 102(b) as anticipated by Simons et al., and Schultz et al.

The Examiner states that Simons describes a method of preventing or treating atherosclerosis, which is the disease caused by LDL in vivo, comprising the administration of Vitamin E.

The Examiner asserts that Schultz discloses the administration of Vitamin E necessarily results in its metabolism to 2,5,7,8-tetramethyl-2(2'-carboxyethyl)-6-hydroxychroman.

In response, Applicants respectfully assert that the Examiner's characterization of the references of Simons and Schultz is in error.

Simons describes the minimum vitamin E dose that will significantly reduce the susceptibility of LDL to oxidation. However, the Simons reference fails to disclose that 2,5,7,8-tetramethyl-2(2'-carboxyethyl)-6-hydroxychroman (α-CEHC) or 2,7,8-trimethyl-2(2'-carboxyethyl)-6-hydroxychroman (γ-CEHC) *per se* has anti-oxidant activity. Furthermore, the Simons reference fails to suggest or to teach that α-CEHC and γ-CEHC may be used directly as anti-oxidant.

Schultz shows that vitamin E can be transformed to hydroxychromane compounds in vivo and 2,5,7,8-tetramethyl-2(2'-carboxyethyl)-6-hydroxychroman (α-CEHC) is detected

in urine after administration of vitamin E. Nevertheless, Schultz reference does not disclose that 2,5,7,8-tetramethyl-2(2'-carboxyethyl)-6-hydroxychroman (γ-CEHC) or 2,7,8-trimethyl-2(2'-carboxyethyl)-6-hydroxychroman (γ-CEHC) *per se* has anti-oxidant activity. Furthermore, Schultz fails to disclose that α-CEHC and γ-CEHC may be used directly as anti-oxidant. It is also not evident in Schultz whether or not the hydroxychromane compound found in urine is an excreting derivative of α-tocopherol.

In the Office Action, claims 1-3 further stand rejected under 35 U.S.C. § 102(b) as anticipated by Christen et al., and Darko et al.

The Examiner states that Christen discloses a method of preventing or treating atherosclerosis, which is the disease caused by LDL in vivo, comprising the administration of Vitamin E and/or γ-tocopherol via diet.

The Examiner also asserts that Darko discloses that γ-CEHC is an oxidative side-chain degradation product of γ-tocopherol.

In response, Applicants respectfully traverse the rejection. Neither Christen reference nor Darko reference discloses that α-CEHC or γ-CEHC *per se* has anti-oxidant activity. Moreover, both references fail to suggest or to teach that α-CEHC and γ-CEHC may be used directly as anti-oxidant.

103 argument

Therefore, the present invention is distinguishable from Simons et al., Schultz et al., Christen et al., and Darko et al. Thus, the rejection is improper and should be withdrawn.

Rejection Under 35 U.S.C. § 103(a)

Claims 4-7 stand rejected under 35 U.S.C. §103(a) as obvious over HerbiesNaturals and U.S. Trademark 2169587 in view of Schultz et al., Christen et al., and Darko et al. The Examiner states that HerbiesNaturals discloses Gamma E+; a medicament comprising α-tocopherol, γ-tocopherol, and mixed tocotrienols having been manufactured. U.S. Trademark 2169587 discloses that data of Gamma E+ first used in commerce as June 1, 1997. The Examiner further states that it would have been obvious to modify the primary reference by employing at least one known metabolite of α-tocopherol, α-tocotrienol, γ-tocopherol, or γ-tocotrienol in the manufacture of a medicament for antioxidant purposes.

The Examiner further asserts that Schultz reference discloses that the administration of Vitamin E necessarily results in its metabolism to α-CEHC; that Darko reference discloses that the administration of γ-tocopherol necessarily results in its metabolism to γ-CEHC; and that Christen reference discloses the necessity of γ-tocopherol in an antioxidant method employing Vitamin E.

In response, claims 4-7 have been canceled. Claims 8-19 have been added. Accordingly, the Examiner's contention is respectfully traversed.

The present invention is directed to a Vitamin E metabolite which has anti-oxidant activity. In contrast, Schultz describes that α-CEHC is found in urine after Vitamin E supplementation. Schultz reference does not show any pharmacological function of the hydoxychromane compound, nor is it clear in the reference whether the hydroxychromane compound found in urine is an excreting derivative of α-tocopherol.

Christen discloses that γ-tocopherol complements the function of α-tocopherol as antioxidant by trapping mutagenic electrophiles such as NO_x. Nonetheless, Christen reference fails to suggest hydroxychromane compounds.

Darko reference discloses that γ-tocopherol can be transformed to hydoxychromane compounds in metabolism and this is the result of modification caused by oxidizing a derivative of γ-tocopherol. Nevertheless, the Darko reference merely shows anti-oxidant function of γ-tocopherol and its oxidized result in place of organs. It fails to suggest the anti-oxidant function of hydroxychromane compounds.

In short, none of the above references disclose that α-CEHC and γ-CEHC have anti-oxidant activity. In addition, none of the references suggest that α-CEHC or γ-

CEHC may be used directly as an anti-oxidant. The Examiner's assertion that one would also have been motivated to use the metabolite in the manufacture of a composition may be characterized as a hindsight.

Thus, the references of HerbiesNaturals, U.S. Trademark 2169587, Schultz et al., Christen et al., and Darko et al do not support a prima facie case of obviousness, and therefore, withdrawal of the 35 U.S.C.§103 rejection is respectfully requested.

CONCLUSION

All of the stated grounds of objection and rejection have been properly traversed, accommodated, or rendered moot. Applicant therefore respectfully requests that the Examiner reconsider all presently outstanding objections and rejections and that they be withdrawn. It is believed that a full and complete response has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone Ping Wang, M.D. (Reg. No. 48,328) at the Office of Birch, Stewart, Kolasch & Birch, LLP.

Prompt and favorable consideration of this Response is respectfully requested.

Attached hereto is a marked-up version of the changes made to the application by this Amendment.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies, to charge payment or credit any overpayment to Deposit Account No. 02-2448 for any additional fees required under 37 C.F.R. §§ 1.16 or 1.17; particularly, extension of time fees.

Respectfully submitted,

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ATTACHMENT

VERSION WITH MARKINGS TO SHOW CHANGES MADE

IN THE CLAIMS:

Claims 4-7 have been canceled.

The claims have been amended as follows:

1. (Amended) A method of preventing or treating a disease caused by oxidation in vivo **[**by**]** , said method comprising a step of administering a pharmacologically effective amount of at least one compound selected from the group consisting of:

(1) 2,5,7,8-tetramethyl-2-(β-carboxyethyl)-6-hydroxychromane, a pharmacologically acceptable salt thereof, or a pharmacologically acceptable hydrate thereof; and

(2) 2,7,8-trimethyl-2-(β-carboxyethyl)-6-hydroxychromane, a pharmacologically acceptable salt thereof, or a pharmacologically acceptable hydrate thereof.

2. (Amended) The method **[**as claimed in the**]** according to claim 1, **[**in which the**]** wherein said disease is **[**that**]** caused by oxidated low density lipoprotein (LDL).

3. (Amended) The method **[**as claimed in the**]** according to claim 1, **[**in which the**]** wherein said disease is arteriosclerosis.

Claims 8-19 have been added.